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An Electrochemical Route for Special Oxidative Ring-Opening of Indoles

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Abstract: A novel electrochemical protocol for the oxidative cleavage of indoles has been developed, which offers a simple way to access synthetically useful anthranilic acid derivatives. In undivided cells, a wide variety of indoles and alcohol compounds are examined to afford amide ester aromatics without using extra oxidants and stoichiometric metal catalysts, which avoids the formation of undesired by-products and exhibits high atom economy. The products we described in this perspective represent a synthetic intermediate in numerous drug molecules and industrial chemical reagents and remarkably show potential application in the future.

Introduction

As a privileged motif, indoles are prevalent molecular architectures that are widely found in natural products.[1] Considering that there have been numerous simple, efficient, and economical methods for the preparation[2] and functionalization[3] of indoles, the discovery of indole ring-fragmentation methods to realize the ortho-functionalization of the phenyl group shows conspicuous significance. Oxidative cleavage of aromatic rings occurs frequently in nature,[4] while oxidation of indoles is a fundamental organic transformation to deliver a variety of synthetically and pharmaceutically valuable nitrogen-containing compounds. The corresponding oxidative cleavage of the C2═C3 bond of indoles was first reported in 1951 by Witkop using Pt/O_2 oxidation.[5] Various oxidants including periodic acid ($NaIO_4$), chromic acid, peracids (m-CPBA), ozone and singlet oxygen, were identified for Witkop oxidation.[6] Subsequently, Kiyoshi Tanaka[7] developed a novel method for the oxidative cleavage of indole carbon double bonds using plant cell cultures as peroxidase in the presence of H_2O_2. In 2016, a transition-metal-free C–C and C–N bond cleavage of 2-arylindoles at 120 °C was developed.[8] Then, the development of methylene blue-catalyzed oxidative cleavage of N-carbonylated indoles was reported by Wang.[9] However, all these methodologies worked towards N-protected indole or indole substituted with electron-donating groups, and did not show any activity towards free indole (Scheme 1). In addition, their environmental influences and atom economy were not addressed, which is contrary to the rising concept and awareness of green chemistry. Recently, Tong[10] developed green oxidation reactions of indoles using halide catalysis and Shoubhik Das[11] achieved visible-light mediated dearomatization of C2-

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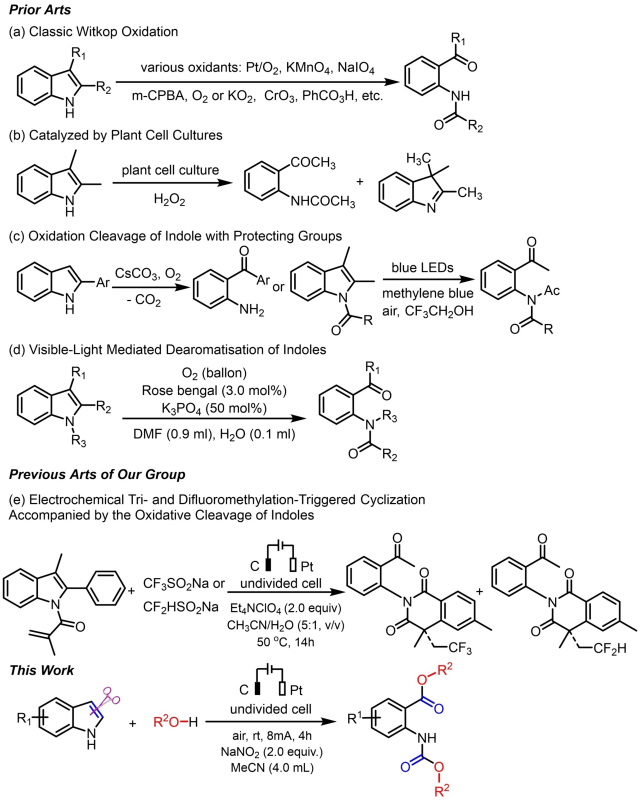


Scheme 1. Oxidative cleavage of indoles: Prior arts and this work.

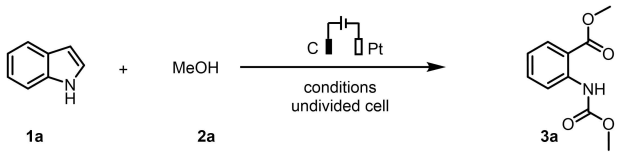
and C3-substituted indoles and then synthesized ortho-formyl/acyl anilide derivatives. Moreover, the realization of ring-opening functionalization of the indoles requires not only strong oxidants but also suitable substitutions at C2 and/or C3 positions, as well as the protecting group on the nitrogen.

In fact, those ortho-formyl/acyl anilide derivatives from the oxidation ring opening of indoles are an important structural motif for the synthesis of natural products and bioactive compounds. Anthranilic acid derivatives are one of the downstream products that have exhibited a broad spectrum of biological activities in the field of medicine and chemical industry. For example, flufenamic acid (classical NSAIDs), an anthranilic acid derivative, demonstrates its anti-inflammatory and analgesic potential.[12] Benzodiazepines and benzotriazepines with anti-anxiety, sedative and hypnotic effects also contain the nucleus of *o*-amidobenzoate.[13] Over the years, numerous synthetic strategies[14] have been developed for the construction of ortho-formyl/acyl anilide derivatives. Unfortunately, traditional methods mostly rely on the use of precious transition metals, or require harsh conditions (high temperature, strong oxidants, and prolonged times), or have possibility for the formation of side products. In addition, it is relatively difficult to selectively introduce amino groups to the ortho position of substituted benzene compounds. The acylation process of amino groups often involves reagents such as acid anhydrides and acid chlorides, which may contaminate the environmental or cause low atom economy problems. Consequently, innovative efforts should be made in the synthesis of ortho-formyl/acyl anilide scaffolds using indole as raw material through environmentally friendly and easy routes. Vodopivecd and co-workers[15] confirmed that electrochemical oxidation of isatin gave a stable and strongly fluorescent main product methyl N-(methoxycarbonyl) anthranilate. Electrochemistry has become an appealing choice towards green oxygenation, which could obviate the participation of transition-metals and strong oxidants. A short time ago, our group have developed an electrocatalytic fluoroalkylation and cyclization indole oxidative cleavage reaction under catalyst- and oxidant-free conditions[16] (Scheme 1). Inspired by the information mentioned above and according to our previous work on indoles,[17] we envisaged the feasibility of realizing the oxidation of indole to isatin and then the cleavage of the latter under external-oxidant-free and catalyst-free conditions using electrochemistry. Herein, we reported a transformation of indoles to advanced products, which were identified as the corresponding anthranilic acid derivatives, through an environmentally responsible electrochemical oxidative ring-opening reaction. The oxidative cleavage of indoles in presence of alcohol leading to the formation of two ester groups was unreported. In this process, our protocol not only eliminates the use of hazardous oxidants (e.g., $PhI(OAc)_2$, CrO_3, $KMnO_4$, and m-CPBA, etc) but also the production of organic by products or toxic heavy metals derived from oxidants to minimize the environmental and health impact of the indole oxidation. In addition, N-unsubstituted indoles, including indole itself, or indoles substituted with electron-withdrawing groups on the benzene part are tolerated in comparison with previous methods.

Results and Discussion

Initially, 1H-indole (**1 a**) was used as a model substrate to start our investigation under constant current (Table 1). Surprisingly, the use of certain electrolytes, such as KBr, KI, Me_4NI, $^nBu_4NI$, $NaNO_2$ and NaCl, could afford an unexpected product, different from that the Witkop oxidation generated. After our careful investigation and analysis, the product obtained was identified as methyl 2-(methoxycarbonylamino) benzoate (**3 a**). Then, the effects of different reaction conditions, including the solvent, electrolyte, equivalent, and electrode were investigated. Firstly, different electrolytes showed that $NaNO_2$ performed better than the others, affording the desired product in 65% yield (Table 1, entries 1–15). Then, the effect of solvent was explored, and the results indicated that the cosolvent of CH_3OH/CH_3CN (v/v = 1/1, 8 mL) showed the best performance (Table 1, entries 16–22). While choosing Me_4NI as the electrolyte, the yield of the product was close to the optimal yield. Use of one rather than two equiv. of sodium nitrite failed to lead to the product **3 a** (Table 1, entry 23), for the possible reason that sodium nitrite, selected as electrolyte, has poor solubility in this system. The

Table 1. Optimization of reaction conditions.[a,b,c]



1a 2a 3a

Entry	Electrolyte (equiv.)	Solvent [8.0 mL]	I [mA]	Temp [°C]	Yield[b,c] [%, **3 a**]
1	$^nBu_4NPF_6$ (2)	$MeOH/CH_3CN$ (1/1)	8	25	0
2	KCl (2)	$MeOH/CH_3CN$ (1/1)	8	25	trace
3	KBr (2)	$MeOH/CH_3CN$ (1/1)	8	25	37
4	KI (2)	$MeOH/CH_3CN$ (1/1)	8	25	48
5	Et_4NClO_4 (2)	$MeOH/CH_3CN$ (1/1)	8	25	0
6	$^nBu_4NOAc$ (2)	$MeOH/CH_3CN$ (1/1)	8	25	0
7	Et_4NCl (2)	$MeOH/CH_3CN$ (1/1)	8	25	6
8	TBAB (2)	$MeOH/CH_3CN$ (1/1)	8	25	34
9	Me_4NI (2)	$MeOH/CH_3CN$ (1/1)	8	25	56
10	Et_4NI (2)	$MeOH/CH_3CN$ (1/1)	8	25	3
11	$^nBu_4NI$ (2)	$MeOH/CH_3CN$ (1/1)	8	25	39
12	I_2 (2)	$MeOH/CH_3CN$ (1/1)	8	25	0
13	$NaHCO_3$ (2)	$MeOH/CH_3CN$ (1/1)	8	25	trace
14	NaCl (2)	$MeOH/CH_3CN$ (1/1)	8	25	7
15	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/1)	8	25	65
16	$NaNO_2$ (2)	MeOH/DCE (1/1)	8	25	32
17	$NaNO_2$ (2)	$MeOH/H_2O$ (1/1)	8	25	0
18	$NaNO_2$ (2)	MeOH/HFIP (1/1)	8	25	0
19	$NaNO_2$ (2)	MeOH (1)	8	25	18
20	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/3)	8	25	21
21	$NaNO_2$ (2)	$MeOH/CH_3CN$ (3/1)	8	25	31
22	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/7)	8	25	trace
23	$NaNO_2$ (1)	$MeOH/CH_3CN$ (1/1)	8	25	8
24	$NaNO_2$ (3)	$MeOH/CH_3CN$ (1/1)	8	25	60
25	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/1)	2	25	trace
26	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/1)	4	25	15
27	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/1)	10	25	60
28	$NaNO_2$ (2)	$MeOH/CH_3CN$ (1/1)	20	25	55

[a] Reaction conditions: Pt plate cathode (10 mm × 10 mm × 0.1 mm) cathode, graphite rod anode (Φ 6 mm), constant current, 1a (0.3 mmol, 1.0 equiv.), electrolyte (2.0 equiv., 0.6 mmol), solvent (8 mL), room temperature, 4 h, undivided cell in air. [b] ^1H NMR yield using CH_2Br_2 as the internal standard. [c] Isolated yield.

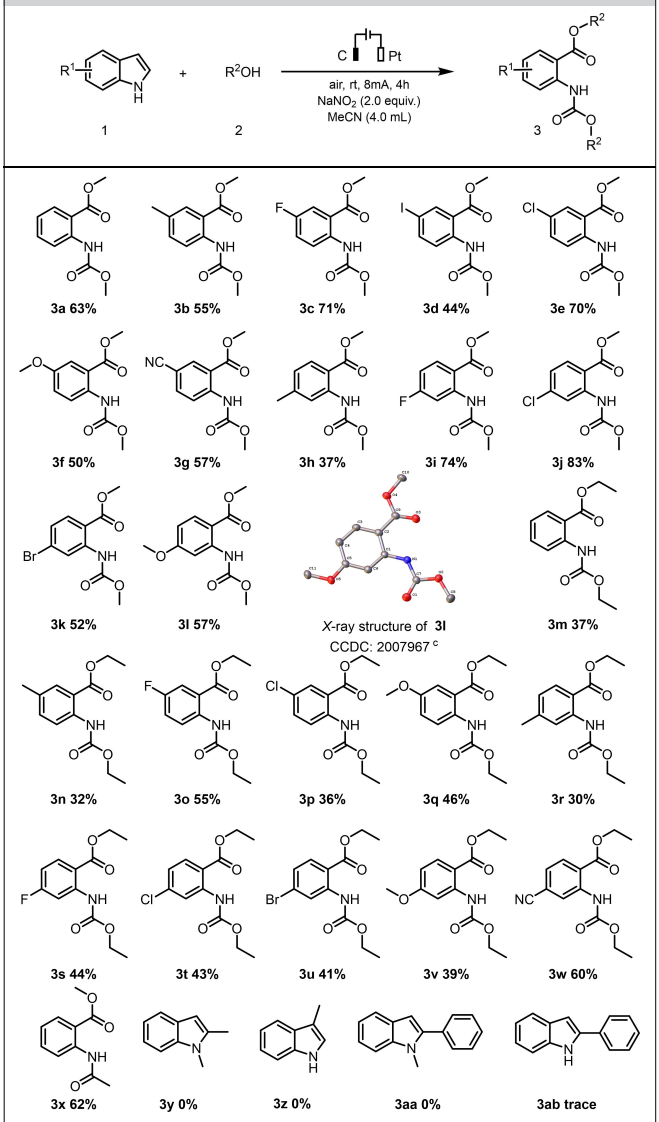
effect of the electrode material was probed. Results showed that replacing the graphite rod anode and Pt plate cathode with other electrode material both produce lower yields (Table S1). Further investigation focused on the electrochemical parameters, either increasing or decreasing the constant current would lead to decreased reaction efficiency. Therefore, the conditions used in entry 15 were selected as the best reaction conditions.

With these optimized reaction conditions in hand, we applied our electrochemical system for the oxidation cleavage of different indole derivatives (Table 2, **3a**–**3w**). Indeed, screening of the substitution showed that indoles with electron-donating groups (Me and OMe) resulted in the significant decrease of reactivity while electron-withdrawing groups (CN, F, Cl, Br and I) worked smoothly. Indoles bearing electron-withdrawing groups, especially 5-Cl (**3e**, 70%) and 6-Cl (**3j**, 83%), demonstrated favorable reactivity and efficiency. Steric and electronic factors can be invoked to account for the fact that good product yields were obtained using indoles with substituents in the C5-, and C6-positions. The indoles bearing C4- and C7-substituent groups yielded almost no corresponding products. In addition, indole derivatives with substitution at C1-, C2-, or C3-position were used as reactants (**3x**–**3ab**). Unfortunately, only C2-substituted indole (**3x**) could give the expected product, which provides valuable clues on the reaction mechanism. We also examined the substrate scope of alcohols such as ethanol, isopropyl alcohol, n-butanol, amyl alcohol, tertbutyl alcohol, benzyl alcohol and HFIP, etc. However, long-chain alcohol, fluoroalcohol and benzyl alcohol were not well tolerated under the optimized reaction conditions. Only methanol and ethanol generated the corresponding derivatives in medium to good yields.

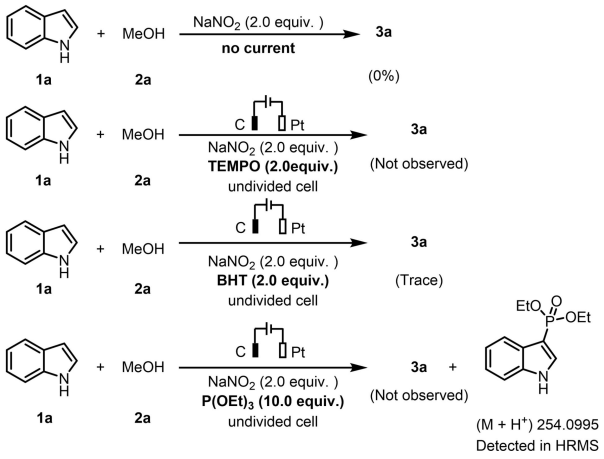
Next, the mechanism of oxidation cleavage of indoles was investigated. A series of control experiments were performed (Scheme 2). Firstly, the reaction of **1a** and methanol was conducted under the standard conditions without current, and there was no desired product detected. When 2.0 equivalents of radical scavenger Tempo (2,2,6,6-tetramethylpiperidine-1-oxyl) or BHT (2,6-*ditert*-butyl-4-methylphenol) were added, there was no product observed. In addition, we added 10.0 equivalents of triethyl phosphate to the system to trap any radical intermediates.[18] The indole-phosphorylation product was obtained, which indicated that an indole radical was produced during the reaction.

Then, we explored the sources of the carbonyl oxygen and methoxy in the product (Scheme 3). Deuterium incorporation suggests that the methoxy group came from methanol. When 20.0 equivalents of $H_2{}^{18}O$ were added, no corresponding oxygen 18 labeled compound was found. When the reaction was conducted under an atmosphere of $^{18}O_2$, compound **3a** was isolated with 100% incorporation of two 18-oxygen atoms which indicates that the two carbonyl oxygens originated from the oxygen. This hypothesis has been confirmed by the fact

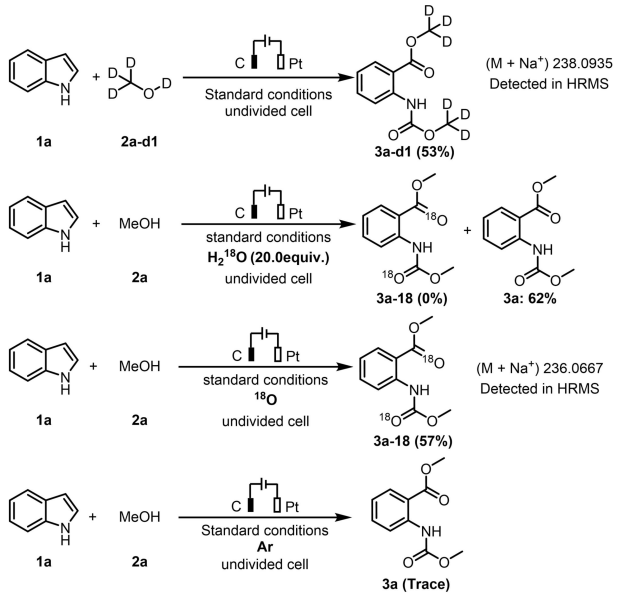
Table 2. Substrates scope for the indoles and alcohol.[a,b]



[a] Reaction conditions: undivided cell, platinum electrode as the cathode (10 mm × 10 mm × 0.1 cm), graphite rod (Φ 6 mm) as the anode, constant current of 8 mA, 1a (0.3 mmol), electrolyte (2.0 equiv., 0.6 mmol), solvent (8 mL, v/v = 1/1), stirred under air at room temperature (25 °C) for 4 h (4.0 F·mol^{-1}). [b] Isolated yields. [c] CCDC: 2007967 (for 3l).



Scheme 2. Control experiments.



Scheme 3. Element source experiment.

that no oxidative cleavage is observed under an argon atmosphere.

Complementary, cyclic voltammetry (CV) experiments (Figure 1) were performed to investigate the redox potential of the substrates, including indole, methanol, $NaNO_2$ and their combination in solution. As shown in Figure 1 (line 1b), no significant oxidation peak of MeOH was observed in the potential window of interest. In contrast, an obvious peak was observed in the CV of indole (line 1a). It is illustrated that indole can be oxidized more easily than MeOH under the optimized conditions, which further excluded the possibility to generate methoxy radicals. As shown in line 1c, we were confused by the appearance of two weak waves at 0.62 V and 2.01 V. Whether $NaNO_2$ has redox potential or participates in the reaction? Therefore, we investigate the combination of $NaNO_2$, MeOH, CH_3CN and indole.

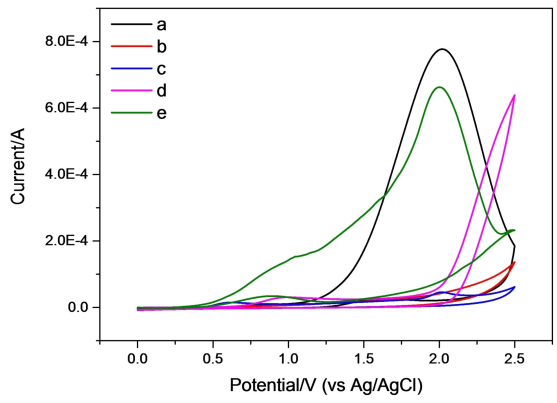
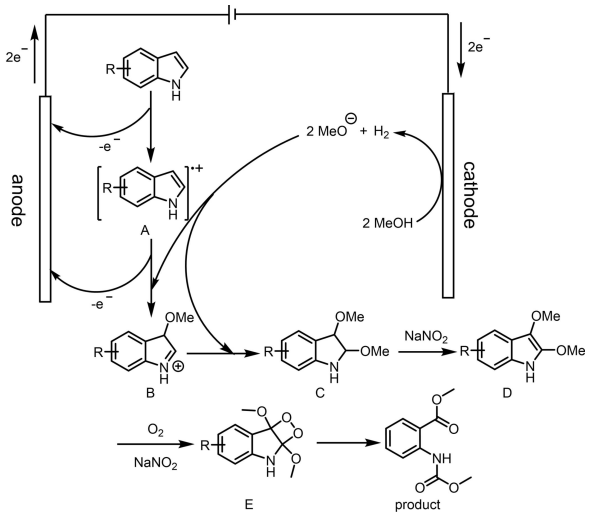


Figure 1. Cyclic voltammograms of substrates: a) 0.3 M Indole, 0.6 M $^nBu_4NPF_6$ in CH_3CN; b) 0.6 M $^nBu_4NPF_6$ in 8 mL MeOH/CH_3CN (1:1); c) 0.6 M $NaNO_2$, 0.6 M $^nBu_4NPF_6$ in CH_3CN; d) 0.6 M $NaNO_2$, 0.6 M $^nBu_4NPF_6$ in 8 mL MeOH/CH_3CN (1:1); e) 0.3 M Indole, 0.6 M $NaNO_2$, 0.6 M $^nBu_4NPF_6$ in 8 mL MeOH/CH_3CN (1:1).

During the experiment, we found that the solubility of $NaNO_2$ in this system is not good and the weak wave at 0.62 was oxidative peak of $NaNO_2$ (see Supporting Information Figure S1). The redox potential of sodium nitrite is lower than that of indole, which is in line with the conditions of indirect electrolysis.[19] Moreover, the oxygen atom source experiment indirectly ruled out the possibility of the formation of C–O bonds between sodium nitrite and indole. In addition to sodium nitrite, the oxidative ring opening of indole can also be carried out using other electrolytes. Sodium nitrite likely acts as an electrolyte like others. Consequently, according to the reference[19] and above experiments, sodium nitrite maybe not only be used as an electrolyte but also a redox mediator which plays the role of transporting electrons during the reaction.

Based on the above experimental results and some related literature,[3,19–20] we propose a reasonable reaction mechanism in Scheme 4. Indole **1a** was oxidized to produce the indole radical-cation intermediate A, which then reacted with the methanol to produce the methoxy indole intermediate B. Then, the resulting iminium ion B was poised to be trapped by a second molecule of methoxide to afford the intermediate C.[3a] Due to the instability of N-unprotected indole, the intermediate C was quickly oxidized to the intermediate D which was then intercepted by molecular oxygen.[21] In addition, a molecular ion peak (m/z = 178.0863) of the intermediate D was detected using Electrospray Ionization-Time-of-Flight-Mass Spectrometry (ESI-TOF-MS) and attributed to [D + H] + (exact mass: 178.0831). (Supporting Information) Subsequently, along with the O–O bond cleavage of four-membered ring E,[22] the C–C bond cleavage led to the final product. Cathodic reduction of methanol affords hydrogen and methoxide, the latter being a critical component at several stages of the proposed mechanism. In the whole process of the reaction, the sodium nitrite is vital to the redox of the indole.



Scheme 4. Plausible reaction mechanism.

Conclusion

In summary, we have developed a novel electrochemical oxidative cleavage of indole derivatives. Combination of ring-opened indoles and alcohols constructs a variety of useful *o*-amidobenzoate building blocks. The reaction involves a mild and facile protocol that occurs without any metals and extra oxidants. The oxidative cleavage of indoles and the incorporation of the alcohol leading to the two ester groups was novel. This methodology provides a convenient scheme for the construction of selective *ortho*-position aryl compounds. Taking the practical application of *o*-amidobenzoate compounds into account, this transformation can be a valuable tool in the preparation of potentially biologically active compounds.

Experimental Section

Crystal-structure analysis: Deposition Number 2007967 (for **3l**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: electrochemistry · oxidative ring opening · transition-metal-free · strong oxidant-free · unsubstituted indoles

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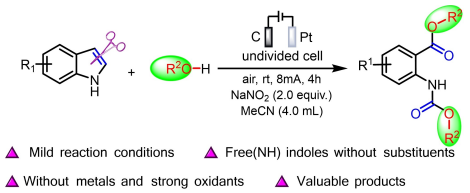

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A novel method of electrochemical oxidation cleavage of indole derivatives and reorganization with alcohols to construct a variety of useful *o*-amidobenzoate building blocks was developed. The reaction involves a mild and easy handling protocol that occurs without any stoichiometric metals and extra oxidants. N-unprotected indoles or indoles substituted with electron-withdrawing groups, even free indole could give the desired product, which expanded the substrate range.